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A 41-Year-Old Woman with Excessive Fat of the Lower Body Since Puberty with Progression to Swollen Ankles and Feet Despite Caloric Restriction, Due to Lipedema and Protein-Calorie Malnutrition: A Case of Stage 3 Lipedema

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Patient: Female, 41-year-old
Final Diagnosis: Malnutrition
Symptoms: Leg edema • weakness
Medication: —
Clinical Procedure: Lymphatic mapping
Specialty: Dermatology • Endocrinology and Metabolic • Surgery

Objective: Rare co-existance of disease or pathology

Background: Lipedema is a common condition that presents as excessive fat deposition in the extremities, initially sparing the trunk, ankles, and feet, and is found mainly in women, usually occurring after puberty or pregnancy. Lipedema can progress to include lipo-lymphedema of the ankles and feet. This report is of a ~~case of stage 3 lipedema and lipo-lymphedema in a case of a~~ 41-year old woman with Stage 3 lipedema and lipo-lymphedema with excessive fat of the lower body since puberty, with progression to swollen ankles and feet despite dietary caloric restriction.

Case Report: A 41-year-old woman noticed increased fat in her legs since age 12. Her weight and leg size increased until age 21, when she reached a maximum weight of 165 kg, and underwent a Roux-En-Y gastric bypass. Over 12 months, she lost 74.8 kg. Her trunk significantly reduced in weight, but her legs did not. Fifteen years later, during recovery from hysterectomy surgery, she became progressively weaker and swollen over her entire body. Laboratory test results showed hypoalbuminemia (2.0 g/dL), lymphopenia, and hypolipoproteinemia. She was diagnosed with protein and calorie malnutrition with marked gut edema requiring prolonged parenteral nutrition. After restoration of normal protein, her health returned and her pitting edema resolved, but her extremities remained enlarged. She was subsequently diagnosed with lipedema.

Conclusions: This report demonstrates that early and correct diagnosis of lipedema is important, as women who believe the condition is due to obesity may suffer the consequences of calorie or protein-calorie deficiency in an attempt to lose weight.

Keywords: Body Mass Index • Kwashiorkor • Lymphedema • Nutritional Physiological Phenomena • Obesity

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Background

Lipedema is a loose connective tissue (LCT) disease characterized by disproportionate accumulation of fibrotic subcutaneous adipose tissue and extracellular fluid in the limbs of women due to microvascular inflammation [1]. Lipedema is poorly recognized and it is often confused with lifestyle-induced obesity [2]. Often, women with lipedema are instructed to reduce caloric intake or increase exercise, neither of which substantially affects lipedema. Lipedema is also often confused with lymphedema, which causes asymmetric swelling of the limbs and is caused by defects in lymphatic transport [3] (**Table 1**). The diagnosis of lipedema is based on the clinical criteria first published by Wold and updated most recently with International Consensus Diagnostic Criteria [4,5] (**Table 2**). These criteria emphasize heavy, tender, symmetric enlargement of the limbs, sparing the hands and feet, with negative Kaposi-Stemmer's Sign. The prevalence of lipedema is not known; however, the most cited estimate of prevalence is 11% of the female population [6]. Lipedema is classified as a diffuse painful symmetric lipomatosis and needs to be differentiated from another lipomatosis disease, called Dercum's disease, which is characterized by painful lipomas [7].

Lipedema progression is graded by stages [3,5,8]. Stage 1 lipedema is characterized by a thickening and disproportionate accumulation of loose connective tissue in the extremities. The skin remains smooth, but there are small palpable nodules in the LCT; the tissue is generally not heavy or swollen, but there may be pain, and there is resistance to weight loss by diet or exercise. Stage 2 lipedema is characterized by increased fibrous tissue leading to larger palpable nodules in the LCT and increased swelling and tenderness of affected areas. Stage 3 lipedema is characterized by formation of lobules of skin and LCT, and larger and more extensive masses in the tissue [8]. Increased tissue sodium and extracellular water are seen in Stage 2 and 3 lipedema [9,10]. Delayed lymphatic transport in lipedema may be present before overt clinical secondary lymphedema or lipo-lymphedema is seen [11,12]. A percentage of women in Stage 3 lipedema develop overt secondary lymphedema with pitting edema in the legs and feet, called lipo-lymphedema [13].

Body mass index (BMI) is commonly used to aid in the diagnosis of diseases. BMI less than 18.5 kg/m^2 is associated with malnutrition. Obesity is often defined as BMI at or above 30 kg/m^2 [14]. Lipedema is often associated with an increased BMI and confused with non-lipedema obesity [2]. However, non-lipedema obesity is often more centrally located, especially around the abdomen or android area, resulting in metabolic

Table 2. Diagnostic criteria for lipedema.

Almost exclusive occurrence in women
Bilateral and symmetrical manifestation with minimal involvement of the feet
Minimal pitting edema
Negative Kaposi-Stemmer sign
Pain, tenderness on pressure
Easy bruising
Persistent enlargement after elevation of the extremities or weight loss
Arms are affected 80% of the time*
Hypothermia of the skin*
Swelling worsens with orthostasis in summer*
Unaffected by caloric restriction*
Telangiectasias*

* Added by Herbst [2].

Table 1. Comparison of findings in lipedema, lymphedema, and lifestyle-induced obesity.

	Lipedema	Lymphedema	Lifestyle-induced obesity
Sex	Women	Women and men	Women and men
Adiposity	Bilateral extremities	Unilateral or bilateral extremities	Whole body, proportionate
	Symmetric	Asymmetric	Symmetric
Edema	Non-pitting	Pitting	None
	Minimal change with elevation; minimal change with compression	Reduced by elevation; reduced with compression (except in late stage)	No change with elevation or compression
Tissue turgor	Soft	Firm	Soft
Pain	Tender to palpation	Usually nontender	None
Infection	Rare	Common	Rare

Shared with permission from author Herbst [3]. Originally published in Buck DW 2nd, Herbst KL. Lipedema: A relatively common disease with extremely common misconceptions. Plast Reconstr Surg Glob Open. 2016;4(9):e1043.

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disease such as type 2 diabetes mellitus (DM2), whereas lipedema is disproportionately located below the waist and also on the arms in gynoid areas, and this pattern is usually cardioprotective [15]. Therefore, defining obesity by increased BMI alone can be inaccurate because it describes 2 very different adipose tissue diseases. This clinical case illustrates that solely using BMI to describe obesity can lead to misleading or inaccurate conclusions. This report is of a case of ~~stage 3 lipedema and lipo-lymphedema in a case of~~ a 41-year old woman with Stage 3 lipedema and lipo-lymphedema with excessive fat of the lower body since puberty, with progression to swollen ankles and feet despite dietary caloric restriction.

Case Report

A 41-year-old woman presented with profound weakness, swelling, and fluid weeping from her legs. The patient reported larger hips and legs since age 12. She continued to gain weight in hips and legs over the next 6 years. At approximately age 18 she began gaining weight all over her body. At age 23 she developed DM2. At that time, her BMI was 62 kg/m^2 [height, 160 cm; weight, 159 kg]. She underwent a Roux-En-Y gastric bypass the following year and lost 61 kg, bringing her weight down to 97.5 kg [BMI, 38 kg/m^2] and resulting in resolution of her DM2. She lost weight primarily in her trunk while her legs remained disproportionately enlarged despite compliance with the post-bariatric diet. Over the next 15 years, numerous physicians recommended additional caloric restriction to correct the disproportionate subcutaneous tissue in her arms and legs. Three years prior to presentation, at age 38, she had a fallopian coil/ESURE placed which was removed a year later by total hysterectomy. Over the year prior to presentation, she lost additional weight to a nadir of 72.6 kg [BMI, 28.3 kg/m^2], after which her weight began to increase as she developed progressive swelling, weakness, sores in her mouth, and loss of appetite. Paradoxically, for 6 months prior to presentation, despite a loss of appetite, her weight increased by 29.5 kg to 97.5 kg. Her weakness progressed to the point that she was falling when attempting to walk across a room. Thereafter, she required a walker to ambulate, and both legs began to leak a clear yellow fluid. She presented to several healthcare facilities, without proper diagnosis. Her past medical history was significant for DM2, hypothyroidism, gastroesophageal reflux disease, fibromyalgia, and depression. Her surgical history included a Roux-En-Y gastric bypass, hysterectomy, cholecystectomy, and inguinal hernia repair. She was a mother of 1 daughter, smoked 2 packs of cigarettes per week and did not drink alcohol. She took the following medications daily: levothyroxine, bumetanide, citalopram, and potassium chloride.

Her exam vital signs were: blood pressure, 110/58; regular pulse at 59 beats per minute; height, 160 cm [5' 3"]; weight, 97.5 kg; BMI, 38 kg/m^2. Her general appearance was as a chronically ill woman with diffuse total body edema. She was unable to walk without the assistance of a walker, and then only for short distances. Her face showed periorbital edema bilaterally and shallow erosions on the tongue and mucous membranes of her mouth. Her lungs were clear and heart rate regular, with normal-sized maximal impulse without displacement. She had diffuse 2+ pitting edema on the legs and trunk. She had trace to 1+ pitting edema on the arms. Her abdomen was soft, mildly distended, mildly protuberant, nontender, and without hepatosplenomegaly. She had disproportionately large arms and legs with cuff signs on both wrists and ankles, consistent with lipedema and/or lymphedema. Her skin exam revealed thin and shiny skin with pitting edema on arms, legs, and abdomen, with small superficial skin ulcerations weeping a clear yellow sticky liquid on both medial ankles. The skin on her hips, legs, and arms was tender to palpation and revealed pea- to walnut-sized subcutaneous nodules consistent with lipedema. Skin lobules, rounded and extruded projections of skin and subcutaneous tissue, were seen at the inner knee, inner thigh, lateral thighs, and upper arms, consistent with Stage 3 lipedema. Her fingernails and toenails were thickened and brittle. She had telangiectasias present on her bilateral lower extremities. Her feet and hands had positive Kaposi-Stemmer signs (inability to tent the skin on the dorsal aspect of the second digit). Laboratory test results are shown in **Table 3**.

Clinical course

The patient was diagnosed with severe protein-calorie malnutrition, anasarca, and Stage 3, ~~t~~ype 3 (waist to ankle), and type 4 (arms affected) lipedema. The hypoalbuminemia caused not only pitting edema of her face, trunk, and extremities, but also gut edema, so that the patient was unable to absorb nutrition properly from her gastrointestinal tract. She was started on parenteral nutrition. As her nutritional state and her serum protein levels improved, her pitting edema resolved and she lost 29.5 kg. Her Kaposi-Stemmers sign reverted to negative in her hands and feet, consistent with lipedema without clinically significant secondary lymphedema. However, mild non-pitting edema in her extremities persisted, which is consistent with lipedema in Stages 2 and 3 of the disease. After several weeks of parenteral nutrition, she was started on enteral and then oral nutrition. Her microcytic iron deficiency anemia, vitamin D deficiency, lymphopenia, and hyperlipoproteinemia all resolved with supplementation and resolution of her gut edema. After stabilization in an acute care setting, she was transferred to a rehabilitation unit to recover her strength and mobility (**Figure 1A, 1B**).

Discussion

This clinical case sheds some insight into the loose connective tissue disease of lipedema, which is dominated by adipose

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Table 3. Laboratory test results.

Test Name	Result	Range
White blood cell	3.0 **(Low)**	3.8-10.8 K/µL
Hemoglobin	9.8 **(Low)**	11.7-15.5 g/dL
Hematocrit	33% **(Low)**	35-45%
Platelet count	380 **(Normal)**	140-400 K/µL
Absolute neutrophils	1700 **(Normal)**	1500-7800 cells/µL
Vitamin D	10 ng/ml **(Low)**	20-40 ng/ml
LDL	65 **(Normal)**	Desirable: < 100 mg/dL
HDL	63 **(High)**	Desirable: < 50 mg/dL
Total cholesterol	153 **(Normal)**	Normal: <200 mg/dL
Glucose	87 mg/dL **(Normal)**	70-120 mg/dL
Albumin	2.0 **(Low)**	3.6-5.1 g/dL
Total protein	5.5 **(Low)**	6.1-8.1 g/dL
Blood urea nitrogen	10 **(Normal)**	7-25 mg/dL
Creatinine	0.6 **(Normal)**	0.5-1.05 mg/dL
Sodium	137 **(Normal)**	135-146 mmol/L
Potassium	3.7 **(Normal)**	3.5-5.3 mmol/L
Chloride	100 **(Normal)**	98-110 mmol/L
Carbon dioxide	22 mmol/L **(Normal)**	20-32 mmol/L
Calcium	8.4 mg/dl **(Low)**	8.6-10.4 mg/dL
Lymphoscintigram	Radiotracer uptake in lymph nodes with slightly delayed clearance in all 4 limbs; interpreted as normal	

LDL – low-density lipoprotein; HDL – high-density lipoprotein.

tissue that can persist in the face of severe protein-calorie malnutrition, and how persistent lipedema tissue can delay a diagnosis of malnutrition. The case also illustrates how edema in lipedema can be multifactorial and switch between non-pitting edema, with no involvement of the feet and hands, to pitting edema, with involvement of the feet and hands. The presence of orthostatic or dependent edema, which usually spares the feet, has been considered a sign of the disease since it was first described by Allen and Hines, but it remains poorly understood [16]. Clinically, on exam, one can appreciate weighty subcutaneous tissue with non-pitting edema in the dependent extremities in women with stage 2 and 3 lipedema. Crescenzi et al showed that there is increased tissue sodium in the lower extremities of women with lipedema on magnetic resonance imaging (MRI), suggesting an increase in glycosaminoglycans, which bind sodium but also water [9]. This increased sodium in the lower extremity skin is present even when there is no free fluid seen in the lower extremities on MRI [9]. This may be one reason why patients with lipedema often have non-pitting edema (the water/fluid is bound to glycosaminoglycans) instead of pitting edema (characterized by increased unbound water/fluid). Increased extracellular water has been shown to be present in the lower extremities, compared with the upper extremities, of women with higher stages of lipedema: Stages 2 and 3 when measured by bioimpedance spectroscopy [10]. Delayed lymphatic transport is also found by lymphangioscintigraphy in patients with lipedema before the overt appearance of clinical secondary lymphedema or lipo-lymphedema [11]. In the case presented here, non-pitting edema was present in the subcutaneous adipose tissue of the lower extremities. This non-pitting edema spared the feet when the patient was in a good nutritional state of health with normal protein levels. This is consistent with the above clinical scientific observations of lipedema. During her state of protein-calorie malnutrition, her feet and hands developed pitting edema, which is also seen in advanced stage 3

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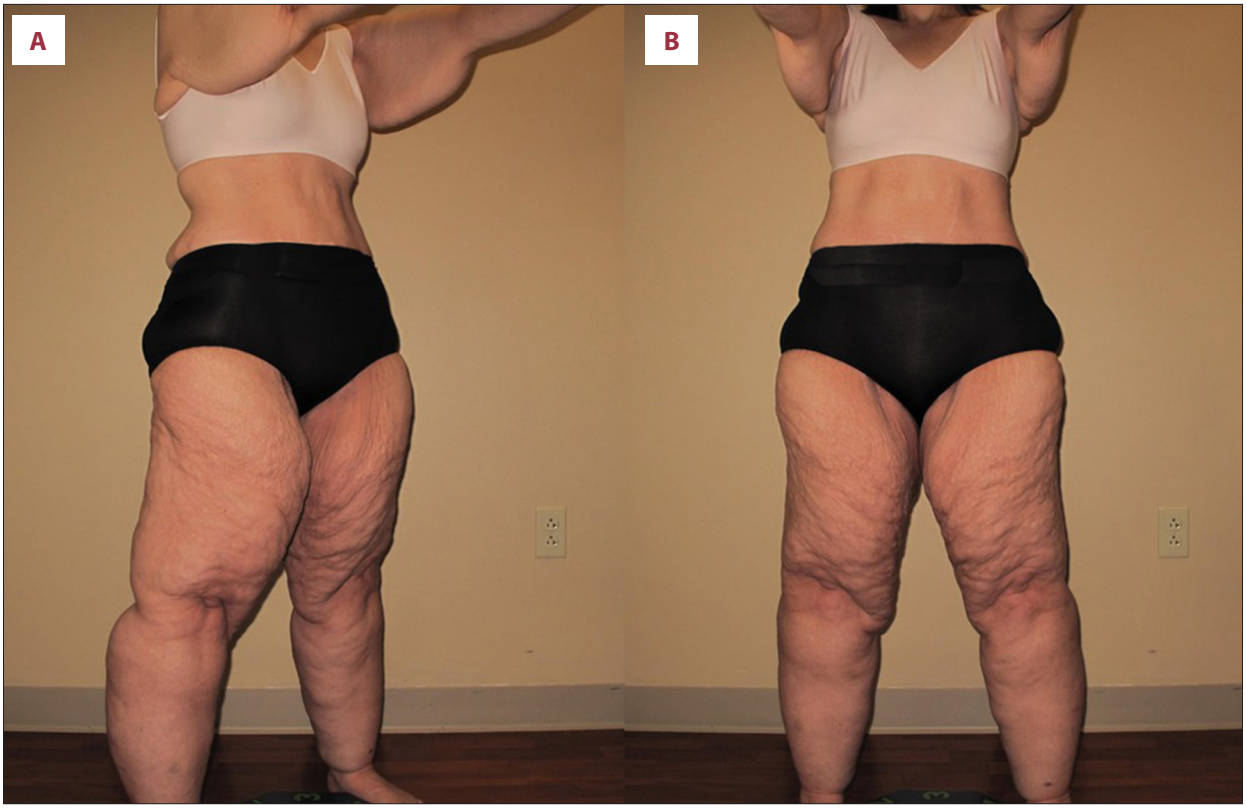

Figure 1. Side (**A**) and front (**B**) views of legs, arms, and torso of a woman with type 3, stage 3 lipedema of the legs and type 4, stage 3 lipedema of the arms. These photos were taken approximately 2 years after presentation to the hospital and after resolution of severe protein-calorie malnutrition and a return to her normal state of health.

lipedema and which is often described clinically as secondary lymphedema and or lipo-lymphedema. In the case presented here, we believe her lymphedema was secondary to her hypoalbuminemia because her lymphoscintigram was interpreted as showing delayed transport but was otherwise normal.

This case illustrates an individual who simultaneously had protein-calorie malnutrition and a BMI over 30 kg/m^2, consistent with obesity. Her increased BMI was largely due to lipedema tissue in the extremities, as her trunk was clearly not obese. Obesity is defined by the World Health Organization [WHO] as abnormal or excessive fat accumulation that presents a risk to health. The WHO further defines a BMI over 25 kg/m^2 as overweight, and BMI over 30 kg/m^2 as obese [14]. The distribution of the patient's excess fat accumulation was not centrally located but was distributed on her hips, arms, and legs. This distribution of fat is not associated with metabolic disease, including cardiovascular disease, hypertension, and diabetes [15]. A better definition of obesity is the Obesity Medicine Association's definition: a chronic, relapsing, multifactorial, neurobehavioral disease, wherein an increase in body fat promotes adipose tissue dysfunction and abnormal fat mass physical forces, resulting in adverse metabolic, biomechanical, and psychosocial health consequences [17].

Lipedema tissue contains hypertrophic adipocytes, similar to non-lipedema obesity, and is associated with lymphedema, similar to non-lipedema obesity [7]. However, the disproportionate fat accumulation in lipedema that confers unique mobility issues is generally not associated with other metabolic effects until later stages [15]. This case shows a woman who, despite her elevated BMI, had hypolipoproteinemia, low-to-normal blood sugar, and other metabolic measures which are considered cardioprotective and not associated with the metabolic changes seen in obesity. BMI is a score and is not an objective measurement of disease-associated fat mass or, more precisely, fat mass-related mechanical and metabolic disturbances. BMI can be elevated by increased nonfat mass such as fluid weight, as seen in this case, or increased muscle mass. In summary, a BMI score, just like the height and weight measurements from which it is derived, is not a biologically representative measure. This case demonstrates how BMI ranges used by the WHO for diagnosis of overweight and obesity can be misleading or biologically wrong, as in this case of a patient with lipedema [18]. Awareness of lipedema among healthcare professionals is poor, and individuals with lipedema are often told they can be treated with caloric restriction, as occurred in this case [19].

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The patient's lymphorrhea and body swelling were secondary to hypoproteinemia and not due to liver, kidney, or heart disease, or even lymphedema. The edema and lymphorrhea resolved after the patient's protein level returned to normal. The patient's lymphoscintigram also did not show evidence of lymphedema, although the clearance of radiotracer was slightly delayed. The slight delay in clearance could have been secondary to hypoalbuminemia or inflammation inhibiting lymphatic vessel pumping [20]. Lipedema is often associated with delayed clearance of radiotracer in lymphangioscintigraphy studies [11,12] and can cause secondary lymphedema, but did not in this case.

Lipedema is characterized by onset and worsening during periods of hormonal changes such as puberty, as occurred in this case [5,8]. The patient's history of worsening of symptoms after her total hysterectomy is also noteworthy. Development or worsening of lipedema is often associated with hormonal changes such as hysterectomy with removal of the ovaries [8]. The patient had a steady weight until her total hysterectomy resulted in worsening of her edema. The nutritional stress of recovering from surgery may also have precipitated protein malnutrition, which can result in gut edema.

The patient's history of a total hysterectomy is noteworthy. Development of lipedema is often associated with hormonal changes such as those seen after hysterectomy with removal of the ovaries [8]. The patient had a steady weight until her total hysterectomy caused worsening of her edema. The nutritional stress of recovering from surgery may also have precipitated protein malnutrition, which can result in gut edema.

Conclusions

This case report demonstrates that an early and correct diagnosis of lipedema is important, as women who believe the condition is due to obesity may suffer the consequences of calorie or protein-calorie deficiency in an attempt to lose weight. This case also illustrates that lipedema can persist even in the face of severe protein and calorie malnutrition and that BMI can be an inaccurate guide for the diagnosis of lipedema, malnutrition, and obesity.

Conflict of interest

None.

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